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Ifosfamide and vinorelbine with G-CSF support-chemotherapy protocol is effective in relapse of Hodgkin's disease

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Introduction. The aim of the study was to evaluate the efficacy and toxicity of a salvage chemotherapy protocol of ifosfamide and vinorelbine in patients with Hodgkin's disease. The protocol had been originally proposed by V. Bonfante et al. of Instituto Nazionale Tumori of Milan at the session of American Society of Clinical Oncology (ASCO) in 1997.
Materials and method. The study group consisted of 15 patients with, at least, stage II of Hodgkin's disease, most of them with early relapse. The majority of patients had extranodal involvement and 10 patients had at least three regimens of chemotherapy before.
Treatment protocol. Ifosfamide 3 g/m^2/day in an 8-hour intravenous infusion for 4 days; uromitexan 3 g/m^2/day in 3 divided doses for 4 days; vinorelbine 25 mg/m^2 on day 1 and day 5; G-CSF support in a standard dose from day 8 to day 14 of the cycle; chemotherapy cycles were repeated every 21 days.
Results. The outlined protocol yielded complete remission in 6 patients, partial remission in 6 patients, stabilisation of the disease process in 2 patients and disease progression in 1 patient. In the complete remission group 3 patients had autologous stem cell transplantation. Treatment toxicity was considered average. The most common side effects included anaemia, neurotoxicity, vomiting, neutropenia and thrombocytopenia. The results of the treatment protocol applied in the pre-selected group of patients may be considered good.

Ifosfamid i vinorelbina z czynnikiem wzrostu G-CSF – schemat skuteczny w leczeniu chorych ze wznową chłoniaka Hodgkina

Wprowadzenie. Celem niniejszej pracy jest ocena skuteczności i toksyczności ratunkowego schematu chemioterapii, składającej się z ifosfamidu i vinorelbiny, u pacjentów z ziarnicą złośliwą. Schemat ten został przedstawiony przez V. Bonfante i wsp. z Narodowego Instytutu Nowotworów w Mediolanie, na zjeździe Amerykańskiego Towarzystwa Onkologii Klinicznej (ASCO) w 1997 r.
Materiał i metoda. Badaniem objęto 15 pacjentów, którzy charakteryzowali się co najmniej II stopniem zaawansowania procesu ziarniczego, w większości ze wczesną wznową. U większości pacjentów stwierdzono umiejscowienie poza węzłowe i w 10 przypadkach chorzy byli po przynajmniej trzech rzutach leczenia cytostatykami.
Schemat leczenia: ifosfamid 3g/m^2/dobę w 8 godzinnym wlewie przez 4 dni; uromitexan 3g/m^2/dobę w 3 dawkach podzielonych przez 4 dni; vinorelbina 25mg/m^2 1. i 5. dnia; czynnik wzrostu G-CSF profilaktycznie w dawce standardowej od 8. do 14. dnia cyklu; kursy powtarzane co 21 dni.
Rezultaty. W wyniku zastosowania powyższego schematu chemioterapii u 6 chorych uzyskano całkowitą remisję, u dalszych 6 chorych – częściową remisję, u 2 – stabilizację procesu, a u 1 – progresję. W grupie pacjentów z całkowitą remisją w 3 przypadkach wykonano przeszczep autologicznych komórek macierzystych z krwi obwodowej. Toksyczność leczenia można ocenić jako średnią. Najczęściej występowały niedokrwistość, neurotoksyczność, wymioty, neutropenia i małopłytkowość. Wyniki, uzyskane w tak wyselekcjonowanej grupie chorych, można uznać za dobre.

Key words: Hodgkin's disease, relapse, ifosfamide, vinorelbine, salvage chemotherapy
Słowa kluczowe: ziarnica złośliwa, wznowa choroby, ifosfamid, vinorelbina, chemioterapia ratunkowa

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Introduction

Most patients with Hodgkin's disease reach a therapeutic success following first-line chemotherapy, often in combination with radiotherapy. Unfortunately, about 20- 40% of patients require salvage chemotherapy because of relapse or resistance to treatment [1].

In 1997, at the session of American Society of Clinical Oncology (ASCO), a team of researchers from Instituto Nazionale Tumori of Milan proposed an alternative salvage chemotherapy in Hodgkin's disease [2]. Promising results of a pilot study encouraged the authors of this report to implement the proposed protocol in patients hospitalised at Department of Chemotherapy of the Oncology Centre of Wielkopolska in Poznań and at the Department of Chemotherapy of the Regional Oncology Centre in Szczecin.

The aim of the study was to evaluate the efficacy and toxicity of salvage chemotherapy protocol of ifosfamide (IFX) plus vinorelbine (VNR) with G-CSF support in patients with Hodgkin's disease.

Materials and methods

In the years 1997-2001 15 patients with Hodgkin's disease hospitalised at Department of Chemotherapy in Oncology Centre of Wielkopolska in Poznań and at Department of Chemotherapy in Regional Oncology Centre in Szczecin were treated according to the IFX plus VNR protocol (Table I). The study group consisted of 10 men and 5 women aged 20 to 49 years (mean age – 29 years). Systemic symptoms of the disease could be observed in 14 patients. In all but 2 patients the histological type of Hodgkin's disease was determined: MC – 6 patients; NS -5 patient (no subtypes were determined); LP – 1 patient; LD – 1 patient. The baseline clinical staging of Hodgkin's disease was as follows: stage IV – 7 patients; stage III – 3 patients; stage II – 5 patients. The first-line chemotherapy yielded sustained remission in 3 patients, short-lasting remission in 6 patients and 6 patients proved resistant to treatment. Before the IFX plus VNR protocol 4 patients had 4 regimens of chemotherapy, 6 patients had 3 regimens, 4 patients had 2 regimens and 1 patient had 1 regimen of chemotherapy. Radiotherapy was utilised in 11 patients. Immediately before the IFX plus VNR protocol 7 patients had extranodal relapse of the disease and 12 patients had ≥3 nodal sites involved. The study participants received from 1 to 6 IFX plus VNR cycles, which amounted to a total of 64 such cycles. Table II shows patient characteristics.

Table I. Treatment protocol [2]

Ifosfamide 3 g/m²/day in 8-hour intravenous infusions for 4 days
Uromitexan 3 g/m²/day in 3 divided doses for 4 days
Vinorelbine 25 mg/m2 on day 1 and day 5
G-CSF as prophylactic support in a standard dose from day 8 to day 14 of each cycle
Cycles were repeated every 21 days

Before IFX plus VNR chemotherapy protocol the study participants had blood morphology tests, biochemistry tests, chest X-ray and/or chest CT, USG and/or CT of the abdomen as well as bone marrow iliac biopsy performed. Objective evaluation of the response to chemotherapy was carried out in compliance with WHO guidelines every 2 cycles. The treatment protocol was as follows: ifosfamide 3 g/m²/day in an 8-hour intravenous infusion for 4 days; uromitexan 3 g/m²/day in 3 divided doses for 4 days; vinorelbine 25 mg/m² on day 1 and day 5; G-CSF support in a standard dose of 5μg/kg from day 8 to day 14 of each cycle. Courses were given at 3-week intervals.

Toxicity was evaluated after each cycle of chemotherapy in compliance with WHO criteria. A subsequent chemotherapy cycle was initiated when toxicity evaluated on day 21 of the cycle was not higher than grade 1. Maximal delay in launching subsequent chemotherapy cycles was 2 weeks. Reduction of 25% in the doses of cytostatics was implemented in case of re-occurrence of grade 3 and grade 4 toxicity on day 21 of each chemotherapy cycle.

Table II. Patient characteristics

Number of patients	15
men	10
women	5
Mean age (years)	29
Range (years)	20 – 49
Systemic symptoms	in 14 patients
Baseline stage of the disease	
stage II	5
stage III	3
stage IV	7
Histological type	
LP	1
NS	5
MC	6
LD	1
none	2
Response to initial therapy	
CR over 12 months	3
CR under 12 months	6
resistance to treatment	6
Earlier radiotherapy	in 11 patients
Number of chemotherapy regimens before IFX plus VNR protocol	
1 regimen	1
2 regimens	4
3 regimens	6
4 regimens	4
Stage of the disease immediately before IFX plus VNR protocol	
extranodal relapse	7
involvement of 3 or more sites	12

CR = complete remission

Results

The IFX plus VNR protocol yielded complete remission in 6 patients, partial remission in 6 patients, stabilisation of the disease process in 2 patients and disease progression in 1 patient. In the complete remission group 3 patients had autologous stem cell transplantation /ASCT/. Up till now 2 patients have reached a 12-month observation period and 1 patient has reached a 6-month observation period. The duration of remission in the remaining 3 patients (without ASCT) spanned 2, 3 and 9 months, respectively.

In the complete remission group 4 patients had stage III and stage IV Hodgkin's disease at baseline,

4 patients experienced relapse after initial therapy and 2 patients were resistant to earlier treatment. Immediately before the IFX plus VNR protocol extranodal relapse (bone marrow, lungs, liver) was confirmed in 5 patients, in 6 patients at least 3 sites were involved and 3 patients had at least 3 regimens of chemotherapy before.

Partial remission (PR) lasted from 2 to 6 months. - Attempts to implement further regimen of chemotherapy failed in 4 patients, yet complete remission, lasting 10 and 20 months, respectively, was obtained in 2 patients.

Complete and partial remission characteristics are presented in Table III.

Toxicity

Anaemia was the most common haematological toxicity and it was observed in 4 patients: grade 3 (3 patients) and grade 4 (1 patient). All those patients required erythrocyte mass transfusions. Stage 2 and stage 3 thrombocytopenia occurred in 3 patients. Despite prophylactic administration of G-CSF grade 3 and grade 4 neutropenia developed in 4 patients and in 3 patients it co-existed with fever. Lower respiratory tract infections developed in 3 patients, upper respiratory tract infections in 2 patients and all those patients required treatment with antibiotics. The most common non-haematological toxicities included grade 2 neurotoxicity in 5 patients and grade 2 and grade 3 vomiting in 6 patients. Grade 2 encephalopathy developed in 1 patient, yet it remitted spontaneously after several days. Renal failure observed in 1 patient was a major adverse effect which required haemodialysis. Adverse effects necessitated dose reduction of cytostatic agents in 4 patients and in 4 patients subsequent chemotherapy cycles had to be delayed.

Discussion

The last 20 years have witnessed major advances in treatment of Hodgkin's disease. The use of MOPP and/or ABVD chemotherapy protocol, often in combination with radiotherapy, as well as introducing new, more aggressive protocols of chemotherapy, e.g. BEACOPP [3] or Stanford V [4], increased the chances for prolonged overall survival.

Despite major success in the treatment of Hodgkin's disease about 20 – 40% of all patients require salvage chemotherapy because of relapse or resistance to first--line chemotherapy [1]. Attempts are being made to find new cytostatic drugs and new chemotherapy protocols effective in the first-line chemotherapy, in salvage chemotherapy and in high dose chemotherapy before autologous stem cell transplantation.

Recently, new salvage chemotherapy protocols, such as MINE [5], MiCMA [6] and CN3OP [7], have been proposed. The researchers from Instituto Nazionale Tumori of Milan have presented their ifosfamide plus vinorelbine protocol results. Both these drugs are active in patients with refractory Hodgkin's disease treated with alkylating agents and vinca alkaloids before. Several phase II studies with vinorelbine report the drug to be active in 35-90% of patients treated with vinblastin and/or vincristine and/or etoposide before [8]. High doses of ifosfamide have also been shown to be effective in patients resistant to standard doses of alkylating agents [9].

The study carried out by the Milan team in the years 1994-1997 comprised 20 patients with Hodgkin's disease, 8 refractory patients and 12 patients with relapse (more than half of them with the second or further relapse). The IFX plus VNR protocol yielded complete remission in 8 patients, partial remission in 8 patients,

Table III. Characteristics of patients with relapse of Hodgkin's disease and with complete or partial remission following IFX plus VNR protocol

Characteristics	Number of patients with complete remission (CR)	Number of patients with partial remission (PR)
Disease stage at baseline		
stage II	2	3
stage III	1	0
stage IV	3	3
Histopathological type		
NS	2	3
MC	3	2
none	1	1
Response to initial therapy		
late relapse	0	2
early relapse	4	1
resistance to treatment	2	3
Site of relapse (immediately before IFX plus VNR protocol)		
nodal sites	1	3
nodal and extranodal sites	5	3
Number of affected sites (immediately before IFX plus VNR protocol)		
at least 3 regions affected	6	6
Number of chemotherapy regimens before IFX plus VNR protocol		
≤2	3	0
> 2	3	6

stabilisation of the disease process in 2 patients and disease exacerbation in 2 patients [2]. The results obtained by V. Bonfante's team and the renown of the institution (G. Bonadonna – one of co-inventors of ABVD protocol is a co-author) encouraged us to try the recommended protocol.

Most of our patients were at an advanced stage of the disease, often with early extranodal relapse, and 10 of them had at least three prior regimens of chemotherapy before. Our results may be considered good and comparable with those obtained by the quoted authors. Particular attention should be paid to characteristics of patients in whom complete remission was obtained (Table III). In this group 4 patients had stage III and stage IV Hodgkin's disease at baseline, 4 patients experienced relapse after initial therapy and 2 patients were resistant to earlier treatment. Extranodal relapse was confirmed in 5 patients, in 6 patients at least 3 sites were involved and 3 patients had at least 3 regimens of chemotherapy before.

Due to relatively good initial results obtained after IFX plus VNR protocol in patients after 3 or 4 earlier chemotherapy regimens one patient had the IFX plus VNR protocol used as salvage chemotherapy (second-line chemotherapy) with subsequent ASCT. Based on the relatively low number of patients in whom the dose of cytostatics had to be reduced the toxicity of the evaluated chemotherapy protocol may be considered average and acceptable. One patient developed irreversible renal failure during the preparatory phase for ASCT and the procedure could not be carried out. The patient had a relapse of Hodgkin's disease after 9 months of complete remission and died because of haemodialysis and chemotherapy complications after 12 months. Transient encephalopathy developed in one patient and manifested with moderate depression, anxiety and somnolence which remitted after several days.

Low number of pre-selected patients participating in the study renders the detailed evaluation of IFX plus VNR protocol difficult, though its efficacy seems to be comparable with the efficacy of other protocols of salvage chemotherapy.

Conclusions

1. Ifosfamide plus vinorelbine protocol is characterised by a high therapeutic efficacy as the third and the fourth chemotherapeutic regimen in Hodgkin's disease and even if applied as fifth-line chemotherapy.
2. Ifosfamide plus vinorelbine protocol is characterised by a high therapeutic efficacy both in stage IV Hodgkin's disease and in refractory Hodgkin's disease.
3. Ifosfamide plus vinorelbine protocol may be used in induction preceding high dose chemotherapy supported by autologous stem cell transplantation.
4. Toxicity of ifosfamide plus vinorelbine protocol may be considered acceptable.
5. The results of ifosfamide plus vinorelbine protocol obtained in the Oncology Centre of Wielkopolska are comparable with those of the pilot study carried out by Instituto Nazionale Tumori of Milan team.

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References

1. Healey EA, Tarbell NJ, Kalish LA et al. Prognostic factors for patients with Hodgkin disease in first relapse. *Cancer* 1993; 71: 2613-2620.
2. Bonfante V, Santoro A, Bonadonna G et al. Ifosfamide and vinorelbine an active regimen potentially effective in detecting sensitive relapses in Hodgkin's disease. *ASCO* 1997
3. Diehl V, Franklin J, Hasenclever D et al. BEACOPP: A new dose-escalated and accelerated regimen is at least as effective as COPP/ABVD in patients with advanced-stage Hodgkin's lymphoma- Interim report from a trial of the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 1998; 16: 3810-3821.
4. Horning SJ, Rosenberg S.A., Hoppe RT Brief chemotherapy (Stanford V) and adjuvant radiotherapy for bulky or advanced Hodgkin's disease: An update. *Ann Oncol* 1996; 7: 105-108.
5. Ferme C, Bastion Y, Lepage E et al. The MINE regimen as intensive salvage chemotherapy for relapsed and refractory Hodgkin's disease. *Ann Oncol* 1995; 6: 517-518.
6. Ortu La Barbera E, Chiusolo P, Laurenti L et al. MiCMA: An alternative treatment for refractory or recurrent Hodgkin's disease. *Ann Oncol* 2000; 11: 867-871.
7. Walewski J, Krzyżanowska JB, Kraszewska E et al. CN3OP: an active regimen in patients with relapsed/refractory Hodgkin's lymphoma. *Med Oncol* 2000; 17(3): 195-202.
8. Devizzi L, Santoro A, Bonfante V et al. Vinorelbine: An active drug for the management of patients with heavily pretreated Hodgkin's disease. *Ann Oncol* 1994; 5: 817-820.
9. Toussaint C, Janin M, Kayitalire L et al. High-dose ifosfamide: circumvention of resistance to standard dose ifosfamide in advanced soft tissue sarcomas. *J Clin Oncol* 1995; 13: 1600-1608.

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